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(21) International Application Number: PCT/US99/03280 (22) International Filing Date: 22 February 1999 (22.02.99) (30) Priority Data: 60/076,710 4 March 1998 (04.03.98) US (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): COLSON, Pierre-Jean [FR/US]; Apartment 1A, 10104 Old Orchard Road, Skokie, IL 60076 (US). AWASTHI, Alok, K. [IN/US]; 9438 Keystone Avenue, Skokie, IL 60076 (US). NAGARAJAN, Srinivasan, R. [US/US]; 16209 Forest Meadows Drive, Chesterfield, MO 63005 (US). (74) Agents: KOVACEVIC, Cynthia, S. et al.; G.D. Searle & Co., P.O. Box 5110, Chicago, IL 60680-5110 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: SYNTHESIS OF CHIRAL β -AMINO ACIDS (57) Abstract <p>The invention herein is directed to a process for the preparation of chiral β-amino acids and esters of formula (I), wherein X and Y are the same or different halo groups, R² is H or lower alkyl and isomers and pharmaceutically acceptable salts thereof.</p> <div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div>		

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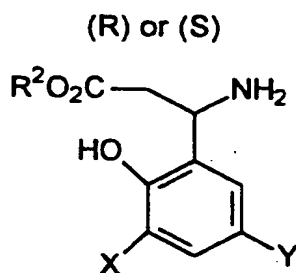
SYNTHESIS OF CHIRAL β -AMINO ACIDS

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Background of the Invention

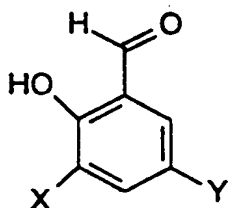
The present invention relates to a process for the preparation of chiral β -amino acids and esters of the formula

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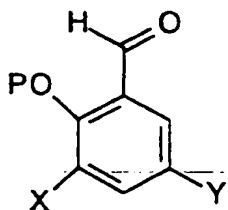
wherein X and Y are the same or different halo group, R^2 is H or lower alkyl; which process comprises reacting a 3,5-dihalosalicylaldehyde of the formula

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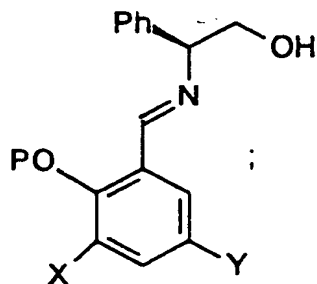


with MEMCl or BnBr (Bn = benzyl) to obtain a protected 3,5-dihalosalicylaldehyde of the formula

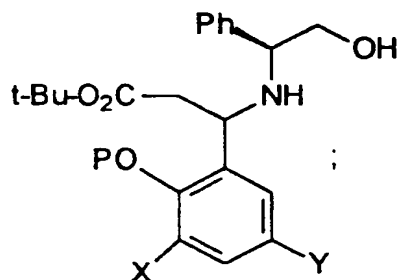
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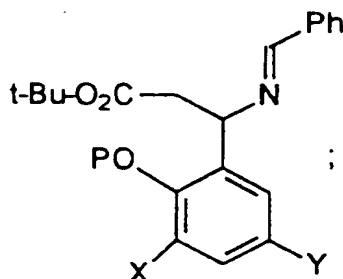
- 5 wherein P is Bn or MEM; treating the protected 3,5-dihalosalicylaldehyde with (R) or (S) phenylglycinol in tetrahydrofuran (THF) or toluene to produce an iminoalcohol of the formula



- 10 reacting said imino alcohol with $\text{BrZnCH}_2\text{CO}_2\text{-t-Bu}$ in N-methylpyrrolidinone (NMP), dimethylsulfoxide (DMSO) or THF to produce an amino alcohol of the formula

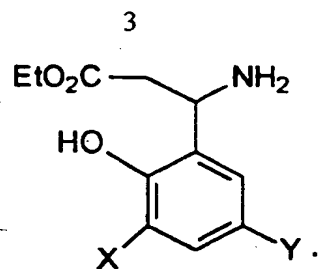


- 15 reacting the amino alcohol with lead tetracetate ($\text{Pb}(\text{OAc})_4$) to form an imine of the formula



- transesterifying, deprotecting, and hydrolyzing said imine in a one pot
20 process to isolate a product of the formula

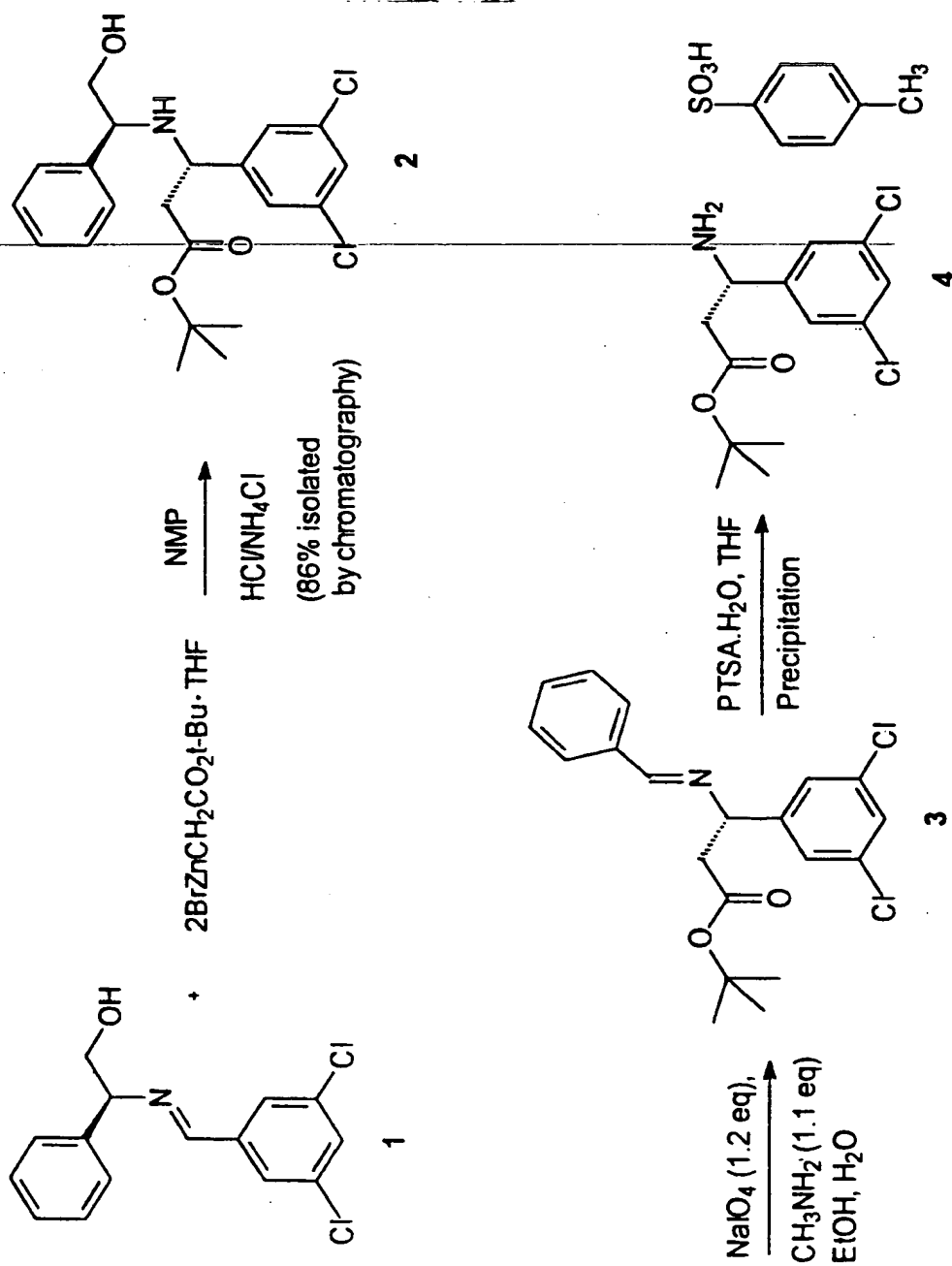
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The reaction provides for the preparation of (R) or (S) isomers with enantiomeric excess (ee) >99%.

USSN 08/890,907 discloses the following process for preparing
10 β -amino acid esters.

Scheme A



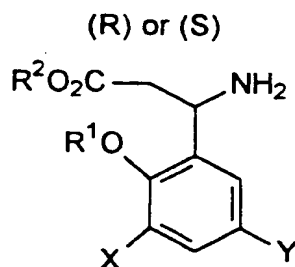
5 Briefly in Scheme A, the chiral imine **1** derived from 3,5-dichlorobenzaldehyde and (S)-phenylglycinol is reacted with 2 equivalents of the Reformatsky reagent ($\text{BrZnCH}_2\text{CO}_2\text{tBu} \cdot \text{THF}$) in NMP at -10°C to afford the corresponding amino alcohol product **2** as one enantiomer (ee>96%). The amino alcohol **2** was then oxidatively cleaved with sodium
10 periodate in ethanol in the presence of methyl amine to afford the corresponding phenyl imine **3**. The β -amino ester **4** was then isolated as a PTSA salt from THF and heptane with an overall yield of 63%.

The chiral β -amino acids and esters produced by the process of the present invention are useful in preparing pharmaceutical agents known as
15 $\alpha_v\beta_3$ integrin antagonists disclosed in W097/08174. It is therefore desirable to provide a process for the preparation of said amino acids and esters which is amenable to scale-up, and which employs raw materials which are readily available, resulting in high yield and a high level of optical purity which doesn't require any chromatography and/or separation
20 of diastereoisomers.

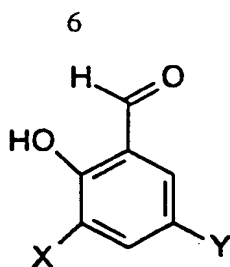
Summary of the Invention

The present invention relates to a process for the preparation of chiral β -amino acids and esters of the formula

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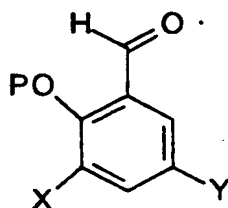


wherein X and Y are the same or different halo group, R^1 is H or
30 methoxyethoxymethyl (MEM) and R^2 is H or lower alkyl; which process comprises reacting a 3,5-dihalosalicylaldehyde of the formula



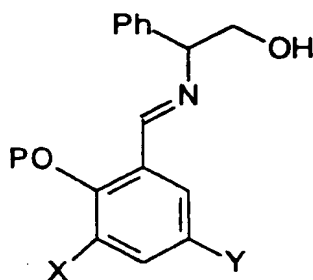
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with MEMCl or BnBr (Bn = benzyl) to obtain a protected 3,5-dihalosalicylaldehyde of the formula



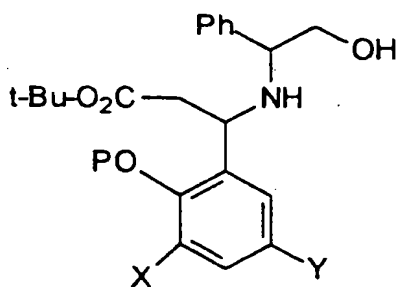
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wherein P is Bn or MEM; treating the protected 3,5-dihalosalicylaldehyde with (R) or (S) phenylglycinol in tetrahydrofuran (THF) or toluene to produce an iminoalcohol of the formula

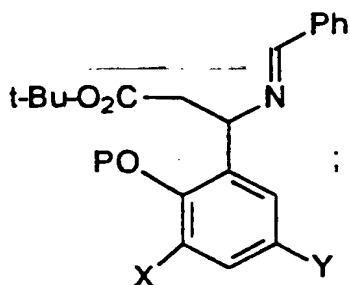


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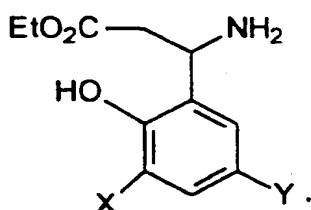
reacting said imino alcohol with $\text{BrZnCH}_2\text{CO}_2\text{-t-Bu}$ in N-methylpyrrolidinone (NMP), dimethylsulfoxide (DMSO) or THF to produce an amino alcohol of the formula



- 5 reacting the amino alcohol with lead tetracetate ($\text{Pb}(\text{OAc})_4$) to form an imine of the formula



transesterifying, deprotecting, and hydrolyzing said imine in a one pot process to isolate a product of the formula



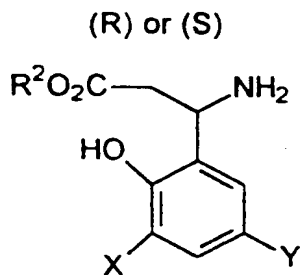
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The reaction provides for the preparation of (R) or (S) isomers with enantiomeric excess (ee) >99%.

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Detailed Description of the Invention

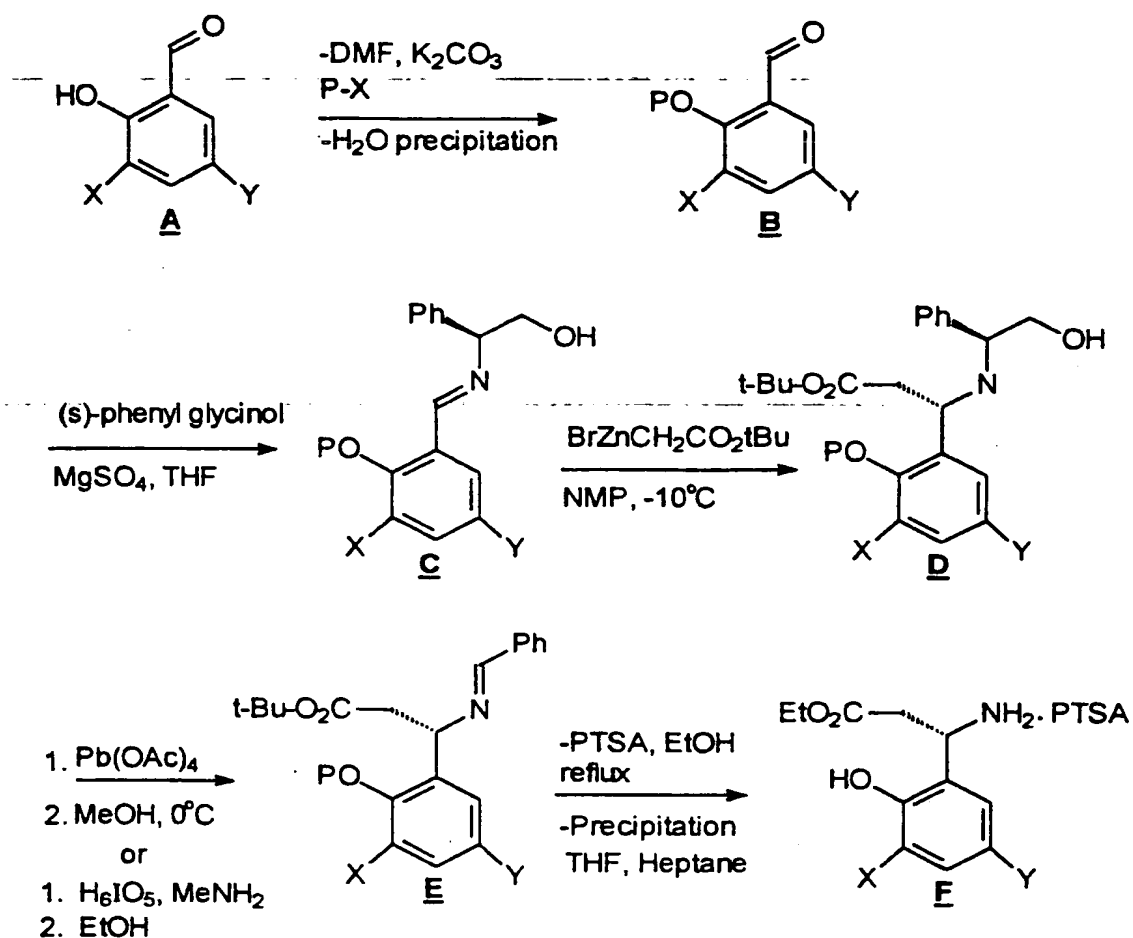
The invention herein is directed to the preparation of β -amino acids and esters of the formula



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and acid addition salts thereof wherein R^2 is H or lower alkyl and X and Y are the same or different halo groups.

Synthetic schemes for the most preferred synthetic methods are outlined in Schemes I-IV and the following descriptions thereof.

SCHEME I

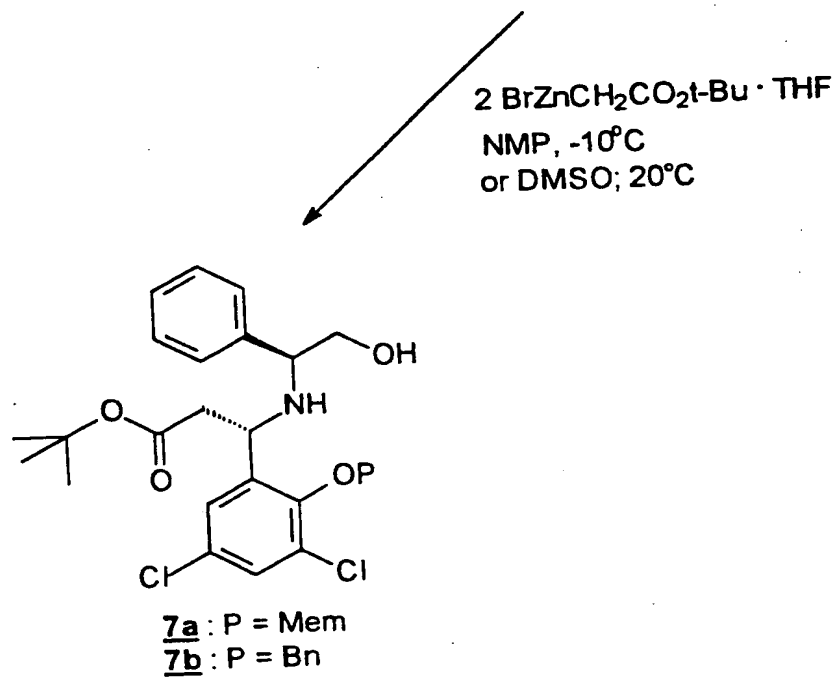
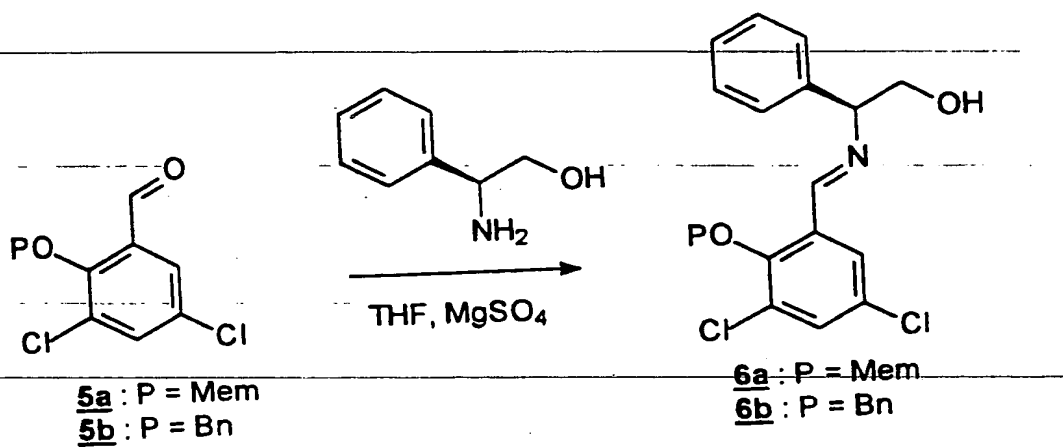
MEM : methoxyethoxymethyl
 Bn : benzyl
 PX = MEMCl or BnBr

P = MEM, Bn
 X = Cl, Br, I
 Y = Cl, Br, I

5 In Scheme I, 3,5-dihalosalicylaldehyde (A, X, Y = Cl, Br, I) was protected as a MEM derivative (B, P = MEM, X, Y = Cl, Br, I) or benzyl derivative (B, P = Bn, X, Y = Cl) by reaction, respectively, with MEMCl or benzyl bromide and potassium carbonate in DMF. The chiral imine C was formed from B and (S)-phenyl glycinol in THF in the presence of
10 magnesium sulfate. C was reacted with two equivalents of Reformatsky reagent ($\text{BrZnCH}_2\text{CO}_2\text{tBu}$.THF) to stereoselectively form D (P = MEM, Bn, X, Y = Cl, Br, I). The amino alcohol residue of D (P = MEM, X, Y = Cl, Br, I) was oxidatively cleaved using lead acetate in methanol to form the
15 imines E (P = MEM, X, Y = Cl, Br, I). Alternatively the oxidative cleavage can be performed with periodic acid in ethanol in the presence of methyl amine. The β -amino esters were then prepared refluxing E (P = MEM, X, Y = Cl, Br, I) in the presence of excess of p-toluenesulfonic acid in ethanol followed by precipitation in THF/heptane. F (X, Y = Cl, Br, I) was obtained with good overall yield and high optical purity and chemical purity.
20 Intermediates C, D, E are not isolated and are used subsequently as prepared without purification.

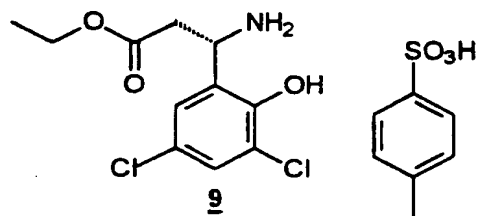
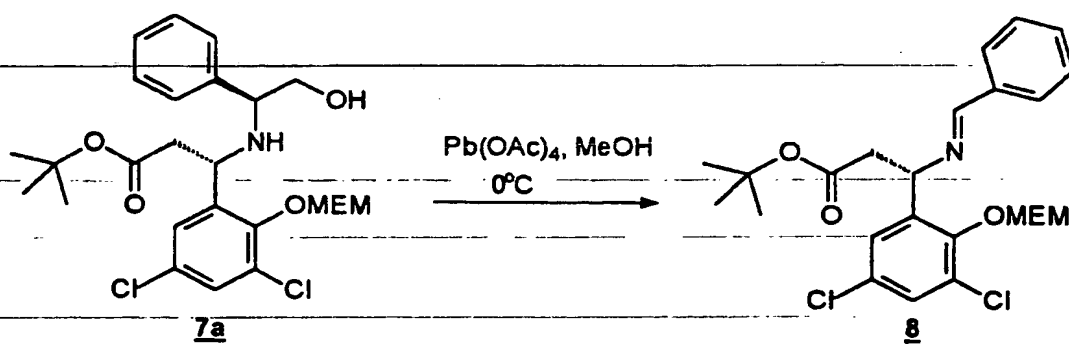
SCHEME II

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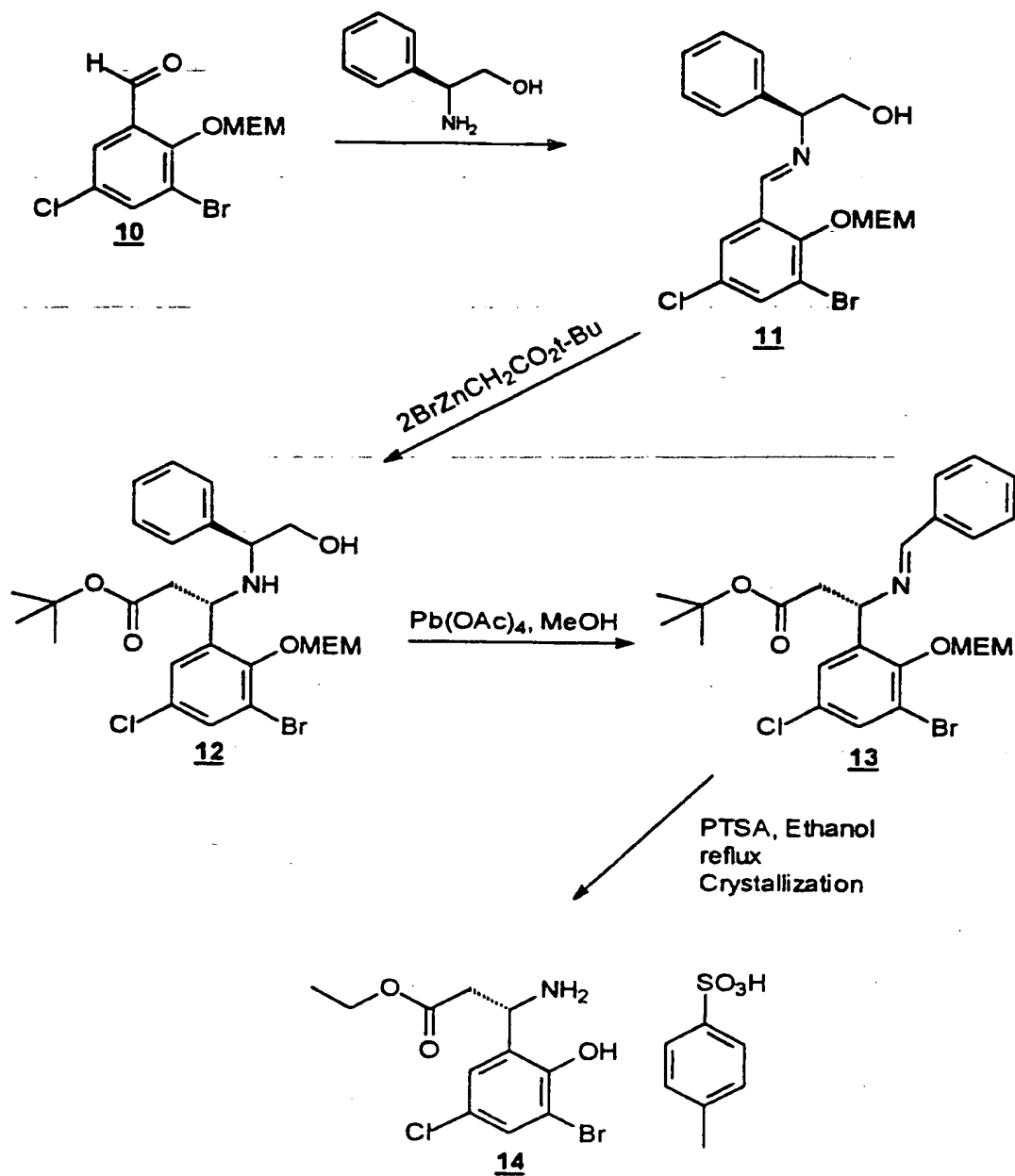
5 In Scheme II, the chiral imines **6a** (P = MEM) and **6b** (P = Bn), were prepared by reaction of the corresponding protected 3,5-dichlorosalicylaldehyde **5a** (P = MEM), **5b** (P = Bn) with (S)-phenyl glycinol in THF in the presence of magnesium sulfate followed by filtration and distillation of the solvent. Imine **6a** was reacted with 2 equivalents of
10 Reformatsky reagent (BrZnCH₂CO₂tBu.THF) in NMP for 1 hour at -10°C followed by quench with HCl/NH₄Cl, extraction with MTBE and distillation of the solvents to obtain a crude product (100%) containing **7a** as one diastereoisomer as determined by ¹H NMR and TLC. The same reaction performed in DMSO at 20°C led to lower selectivity as **7a** is isolated as a
15 95/5 mixture of diastereoisomer with 86% yield after chromatography. Reaction of imine **6b** (P = Bn) in NMP was slower and was completed after 15 hours at -5°C. Compound **7b** was isolated as one diastereoisomer as determined by ¹H NMR and TLC.

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SCHEME III

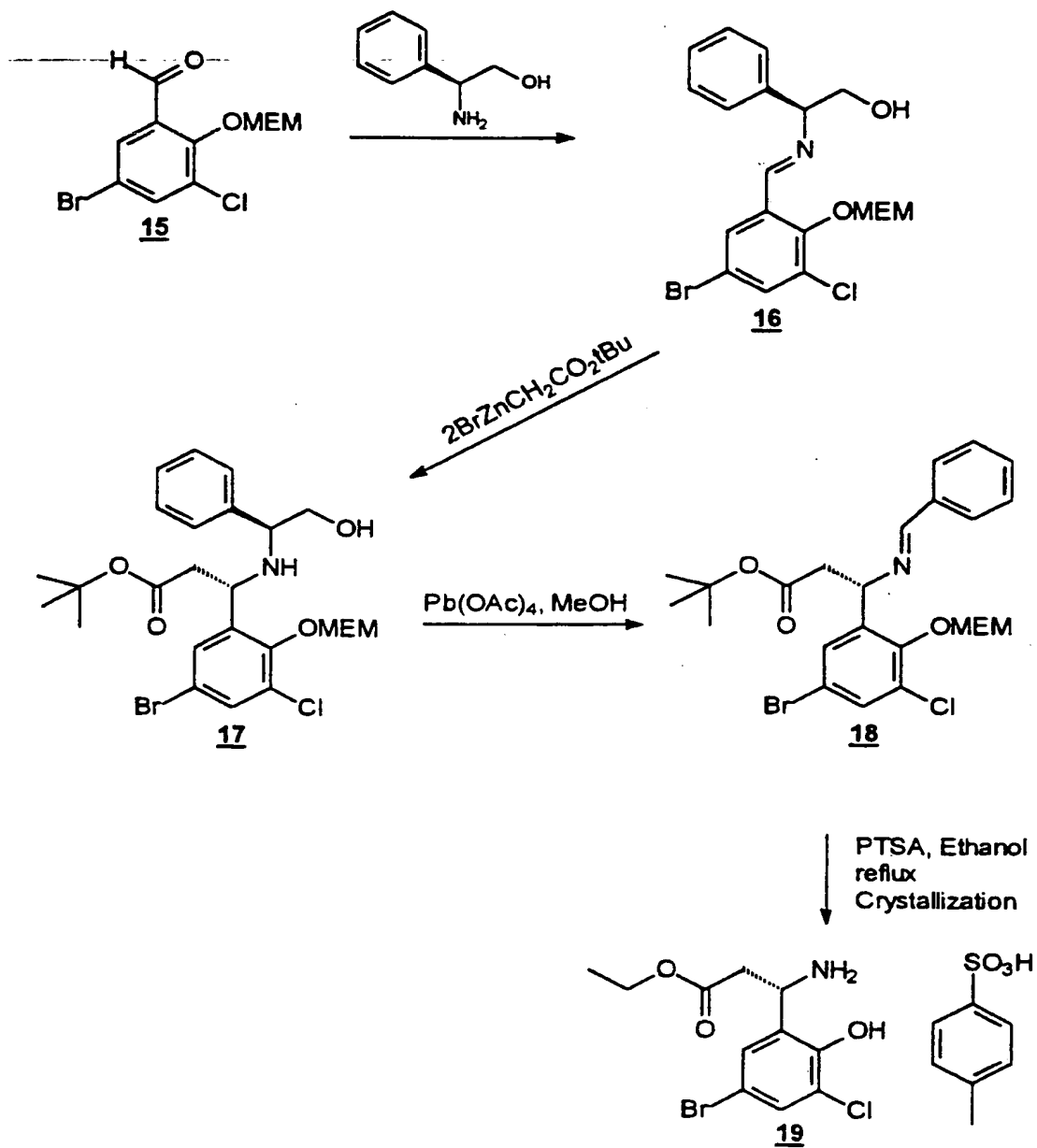
PTSA, Ethanol
reflux
Crystallization

- 5 In Scheme III, the amino alcohol residue of **7a** was oxidatively cleaved using lead tetra acetate in methanol to form the imine **8**. **8** is refluxed in the presence of excess of p-toluenesulfonic acid in ethanol followed by precipitation in THF/heptane. The β -amino ester **9** was obtained with 49% overall yield and ee>99% as determined by chiral LC.
- 10 Alternatively, the oxidative cleavage was performed with sodium periodate in ethanol in the presence of methyl amine or periodic acid in ethanol in the presence of methyl amine.
-

SCHEME IV

5 In Scheme IV, the chiral imine **11** was prepared by reaction of the
corresponding protected 3-bromo-5-chlorosalicylaldehyde **10** with (S)-
phenyl glycinol in THF in the presence of magnesium sulfate followed by
filtration and distillation of the solvent. Imine **11** was reacted with 2
equivalents of Reformatsky reagent in NMP at -10°C followed by quench
10 with HCl/NH₄Cl, extraction with MTBE and distillation of the solvents to
obtain a crude product (100%) containing **12** as one diastereoisomer (as
determined ¹H NMR). The amino alcohol residue of **12** was oxidatively
cleaved using lead acetate in methanol to form the imine **13**. **13** was
refluxed in the presence of excess of p-toluenesulfonic acid in ethanol
15 followed by precipitation in TF/heptane. The β-amino ester **14** was
obtained with 45% overall yield (from unprotected salicylaldehyde) and
ee>99% as determined by chiral LC.

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SCHEME V

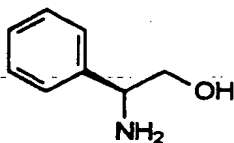
5 In Scheme V, the chiral imine **16** was prepared by reaction of the
corresponding protected 3-chloro-5-bromo salicylaldehyde **15** with (S)-
phenyl glycinol in THF in the presence of magnesium sulfate followed by
filtration and distillation of the solvent. Imine **16** was reacted with 2
equivalents of Reformatsky reagent in NMP at -10°C, followed by quench
10 with HCl/NH₄Cl, extraction with MTBE, and distillation of the solvents to
obtain a crude product (100%) containing **17** as one diastereoisomer as
determined by ¹H NMR. The amino alcohol residue of **17** was oxidatively
cleaved using lead acetate in methanol to form the imine **18**. **18** was
refluxed in the presence of excess of p-toluenesulfonic acid in ethanol
15 followed by precipitation in THF/heptane. The β-amino ester **19** was
obtained with 33% overall yield (from unprotected salicylaldehyde) and
ee>99% as determined by chiral LC.

5 Unless otherwise noted the starting materials for the process of this invention are all commercially available or can be prepared according to conventional methods known to those with skill in the art. All equipment employed is commercially available.

The following is a list of definitions and abbreviations used herein:

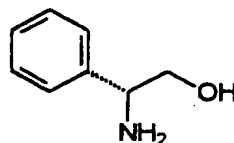
10 The terms "alkyl" or "lower alkyl" refer to straight chain or branched chain hydrocarbon radicals having from about 1 to about 6 carbon atoms. Examples of such alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, hexyl and the like.

The term "L-phenylglycinol" refers to a radical of the formula



and is used interchangeably with the term (S)-phenylglycinol.

The term "D-phenylglycinol" refers to a radical of the formula



20 and is used interchangeably with the term (R)-phenylglycinol.

The term "halo" as used herein refers to a bromo, chloro or iodo radical.

	Ph	=	phenyl
	DI	=	deionized water
25	MEMCl	=	methoxyethoxymethylchloride
	g	=	grams
	L	=	liter
	ml	=	milliliter

ee means enantiomeric excess

30 Bn refers to a benzyl radical

MEM refers to a methoxyethoxymethyl radical

- 5 THF refers to tetrahydrofuran
 NMP refers to N-methylpyrrolidinone
 DMSO refers to dimethylsulfoxide
 NaIO₄ refers to sodium periodate
 NH₄Cl refers to ammonium chloride
10 CH₃NH₂ refers to methylamine
 EtOH refers to ethanol
 Pb(OAc)₄ refers to lead tetraacetate
 PTSA refers to para-toluenesulfonic acid
 MTBE refers to methyl tert-butyl ether
15 NaOEt refers to sodium ethoxide
 EtOAc refers to ethyl acetate
 MgSO₄ refers to magnesium sulfate
 GC refers to gas chromatography.

 The present invention provides a safe, convenient and cost effective
20 manufacturing process for the preparation of chiral β-amino acids and
 esters which is amenable to scale-up. The process utilizes raw materials
 which are readily available and cost efficient. Its convenience is
 demonstrated in that the synthetic route does not require either a
 chromatography or chemical or enzymatic separation of diastereoisomers.
25 Its cost effectiveness is demonstrated by the final products being produced
 in high yield and a high level of optical purity.

 The following non-limiting examples describe and illustrate a
 method for carrying out the process of the present invention, as well as
 other aspects of the invention, and the results achieved thereby in further
30 detail. Both an explanation of, and the actual procedures for, the various
 aspects of the present invention are described where appropriate. These
 examples are intended to be illustrative of the present invention, and not
 limiting thereof in either scope or spirit. Those of skill in the art will readily
 understand that known variations of the conditions and processes
35 described in these examples can be used to perform the process of the
 present invention.

Example 1Preparation ofStep A

- 10 A 4 liter jacketed flask, fitted with a condenser, temperature probe, mechanical stirrer, was charged with 180 g of Zn metal (-30-100 mesh, 180.0 g, 2.76 moles) and 1.25 L of THF to the vessel. While stirring, 1,2-dibromoethane (4.74 ml, 0.05 mole) was added to the vessel via a syringe at once. After purging three times (N₂/vacuum), the suspension of zinc in
- 15 THF was heated to reflux (65°C) and maintained at this temperature for 1 hour. The mixture was cooled to 50°C before charging the tert-butyl bromoacetate (488 g, 369 ml, 2.5 mmole) over a 1.5 hour time period. Controlled reagent addition was done by 50 ml syringe and syringe pump (addition rate set at 4.1 ml/minutes). A temperature of 50°C +/- 5°C was
- 20 maintained during the addition. The reaction mixture was allowed to stir at 50°C for 1 hour after the addition was complete. The reaction mixture was then allowed to cool to 25°C, and upon reaching this temperature the agitation was turned off to allow the precipitated product to settle (the product precipitated from THF solution at 31°C). The THF mother liquor
- 25 was removed by decantation into a 2 L round-bottom flask. which was under partial vacuum (20 mm Hg) with a dip tube (coarse fritted glass filter). This procedure removed 65% of THF from the vessel. 800 ml of NMP is added and agitation is resumed for 5 minutes at 25°C. The reaction mixture was transferred to another vessel by filtration to remove
- 30 the remaining zinc. Analytical determination of the titer was 1.57 Molar with a molar yield of 94%, following the titration method.
- Note:** The solid reagent can be filtered and dried under N₂ using a pressure funnel. The cake was washed with THF until obtaining a white solid. The solid was dried for 1-2 hours. Typical recovery is 85-90%.
- 35 The solid can be stored at -20°C for at least 6 months.

5 **Step B** - Titration method

A 1.0 ml aliquot of the Reformatsky-NMP/THF solution was removed from the reaction mixture via syringe and added to a 25 ml round-bottom flask which contained a pre-weighed amount of benzaldehyde (250-300 mg) and a magnetic stir bar, under a nitrogen atmosphere. The reaction mixture was stirred for 30 minutes at room temperature. To the flask was added 5.0 ml of aqueous 29% NH_4Cl and 5.0 ml of MTBE. The resulting mixture was stirred for 5 minutes at room temperature. The agitation was stopped and the layers allowed to separate over 5 minutes. A 1.0 ml aliquot of the organic layer was removed and diluted to 25 ml with MTBE in a volumetric flask. This solution was subjected to GC analysis using an HP-1 10 m column. Standard solutions of benzaldehyde in MTBE at concentrations of 0.04 M, 0.01 M, and 0.002 M were co-injected with the sample. The sample concentration was determined from the linearity plot of the standard solutions and the sample GC peak area. The concentration of the Reformatsky solution was then determined by using the following calculation:

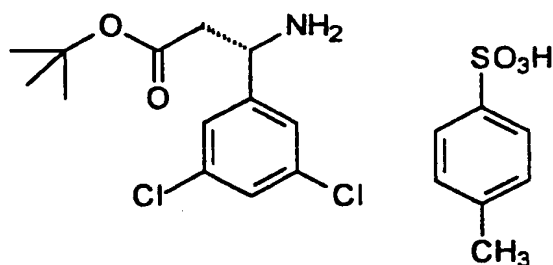
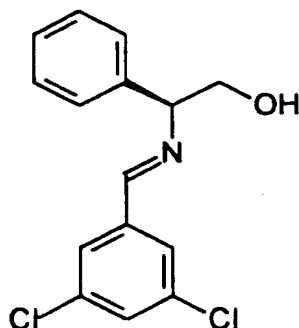
$$\text{Amount of remaining benzaldehyde} = \text{concentration of sample (g/L)} * 50 * 5/2$$
$$\text{Titer (Mole/L)} = \frac{\text{Pre-weighed amount of benzaldehyde} - \text{amount remaining}}{106}$$

Yield = Mole/liter * Total volume of solution / Theoretical 100% yield

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Example 2

Preparation of

Step AFormation of the imine

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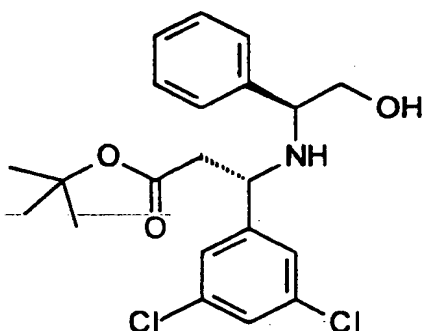
(S)-Phenyl glycinol (11.74g, 0.086 Mole) was charged in a 500 ml 3N round-bottom flask fitted with a mechanical stirrer, followed by toluene (110 ml) and the flask was vacuum/flushed with nitrogen. 3,5-dichlorobenzaldehyde was then added at once. After 15 minutes at 22°C, MgSO₄ (15 g) was added. The mixture was stirred for 1 hour at 22°C, and filtered on a coarse fritted filter. The cake was washed with toluene (20 ml). The solutions were combined and concentrated under reduced pressure to afford 27.00 g of a pale yellow oil containing the imine. No further purification was performed and the crude product was used directly in the coupling reaction. ¹H NMR (CDCl₃, TMS) mixture of imine and oxazoline 4/1. (ppm):(imine) 3.88 to 3.99 (m, 2H), 4.50 (dd, 1H, J = 4.7, 8.1 Hz), 7.67 (d, 2H), 8.28 (s, 1H); oxazoline: 5.55 and 5.70 (s, 0.5 + 0.5 H), 3.72 to 3.83 (m, 0.5 + 0.5 H), 4.30 to 4.35 (m, 0.5 + 0.5 H), 4.40 to 4.48 (m, 0.5 H), 4.54 to 4.60 (m, 0.5 H), mixed protons: 7.15 to 7.47 (m(aromatic + CDCl₃)); ¹³C NMR (CDCl₃, TMS) (ppm):imine: 67.55, 76.38, 135.13,

25

- 5 138.70, 140.05, 159.72. Oxazoline: 60.60, 62.80, 72.12, 72.34, 91.05, 91.68, 135.03, 135.41, 142.62. Mixed signals: (aromatics) 124.86, 124.956, 125.33, 126.53, 126.65, 126.75, 127.38, 127.74, 127.77, 128.11, 128.26, 128.32, 128.72, 128.84, 128.93, 129.06, 130.64.

10 Step B

Reformatsky coupling



- A 1L jacketed 3 ports reactor with bottom valve, fitted with a
- 15 mechanical stirrer and an addition funnel was charged with a solution of Reformatsky reagent from Example 1. The solution was then cooled to -10°C. A solution of imine in NMP (60 ml) was prepared under nitrogen and charged in the addition funnel. The solution of imine from Step A was then added over 5 minutes while the temperature was maintained at -5°C
- 20 (jacket at -10°C). The reaction was monitored by GC and TLC (elution heptane/EtOAc 30%). After 5 minutes the reaction was almost complete (trace of starting material). The mixture was stirred for an additional hour and a mixture of 2N HCl/saturated solution of NH₄Cl (1/2, 135 ml) was added. MTBE (200 ml) was added and the mixture was stirred for 1 hour
- 25 at 23°C. Stirring was stopped and the layers were separated. The aqueous layer was extracted with MTBE (100 ml). The two organic layers were combined, washed successively with a saturated solution of NH₄Cl (140 ml), water (140 ml) and brine (140 ml). The solution was dried with
- 30 MgSO₄ (30 g), filtered and concentrated to afford 35.2g of an orange oil containing the desired product as a single diastereoisomer (by ¹H NMR).

5 In a separate reaction (28.6 mmole scale) the crude product (11.36 g) was purified by chromatography [(SiO₂, 200 g), elution heptane/EtOAc 30%] to afford the desired compound as a pale yellow oil (10.07 g, 85 %).
1H NMR (CDCl₃, TMS) (ppm) 1.40 (s, 9H), 2.56 (dd (AB), 1H, J = 5.6, 15.4 Hz), 2.56 (dd (AB), 1H, J = 8.1, 15.6 Hz), 2.60 (s(broad), 1H), 3.62 (dd
10 (AB), 1H, J = 6.8, 10.7 Hz), 3.72 (dd, 1H, J = 4.2, 6.8 Hz), 3.80 (dd (AB), 1H, J = 4.2, 6.8 Hz), 4.11 (dd, 1H, J = 5.8, 7.9 Hz), 7.09 to 7.29 (m, 8H, (aromatic)); 13C NMR (CDCl₃, TMS) (ppm): 28.00, 42.98, 57.28, 62.24, 65.99, 81.42, 125.69, 127.21, 127.35, 127.60, 128.48, 134.83, 140.78, 146.44, 170.58; DSC: 241.46°C (endo. 180.1 J/g); [α]_D²⁵ = +6.9° (c =
15 1.025, CHCl₃); IR (MIR) (cm⁻¹) 1726, 1587, 1567. Microanalytical: calcd for C₂₁H₂₅Cl₂NO₃: C: 61.47%; H: 6.14%; N: 3.41%; Cl: 17.27 found: C: 59.53%; H: 6.01%; N: 3.05%; Cl: 16.79.

Step C

20 Oxidative cleavage and Salt formation

A solution of crude ester obtained in Step B in EtOH 2B (140 ml) was charged to a 500 ml round-bottom, 3N flask. A solution of methyl amine (8.9 ml, 0.1 mole) was added. A slurry of NaIO₄ (0.112 mole, 25.92 g) in H₂O (72 ml) at 25°C was added by portion while maintaining a
25 temperature of 30°C (+/- 2°C). The reaction was monitored by TLC. The reaction mixture was then stirred at room temperature for 15 hours, NaIO₄ (6 g, 0.026 mole) solid was added. After 4 hours, NaIO₄ (6 g, 0.026 mole) solid was added and the mixture was heated at 30°C for 0.5 hour. After cooling to 25°C, the reaction mixture was concentrated under reduced
30 pressure (water aspirator). MTBE was added and the mixture was filtered through a coarse glass frit filter. The layers were separated and the organic layer was washed with H₂O (100 ml, dried with MgSO₄ (25 g), filtered and concentrated under reduced pressure to afford 30.2 g of an orange oil.

35 The crude mixture was diluted with THF (65 ml) and was charged in a 500 ml round-bottom, 3N flask fitted with a mechanical stirrer and an

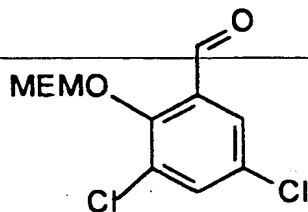
- 5 addition funnel. A solution of p-toluenesulfonic acid monohydrate in THF (20 ml) was then added in 2 minutes followed by a wash of THF (5 ml) via the addition funnel. After 5 minutes, heptane (65 ml) was added at once and heavy precipitation occurred. Heptane (65 ml) was added again.
- After 0.5 hour, the slurry was filtered through a coarse glass frit pressure
- 10 filter and was washed with heptane/THF 20% (100 ml) and heptane/THF 33 % (150 ml). The cake was then dried under vacuum/nitrogen for 2 hours. The ivory solid was collected to afford the desired product (25.1 g).
- ¹H NMR (CDCl₃, TMS) (ppm) 1.26 (s, 9H), 3.37 (s, 3H), 2.84 (dd, (AB), J = 9.5, 16.3 Hz), 2.98 (dd,(AB), J = 5.2, 16.2 Hz), 4.53 (m, 1H), 7.14 (d, 2H, J = 7.9 Hz), 7.19 (t, 1H, J = 1.8 Hz), 7.32 (d, 2H, J = 8.1 Hz), 7.56 (d, 2H, J = 8.1 Hz), 8.43 (s(broad), 3H); ¹³C NMR (CDCl₃, TMS) (ppm): 21.37, 27.80, 39.47, 51.36, 81.85, 125.77, 126.43, 129.01, 129.06, 135.17, 139.14, 140.59, 140.69, 168.06. DSC: 120.30°C (80.71 J/Kg), 242.63°C (endothermic, 100.3 J/g) [α]₂₅^D = +37.4° (c = 0.147, CHCl₃); IR^v (MIR) (cm.⁻¹) 1726, 1587, 1567.
- 20

Microanalytical: found for C₂₀H₂₅Cl₂NO₂S:

C: 51.95%; H: 5.45%; N: 3.03%; Cl: 15.33%; S: 7.02%.

found: C: 51.65%; H: 5.64%; N: 3.01%; Cl: 15.13%; S: 7.00 %

5

Example 3Protection of 3,5-Dichlorosalicylaldehyde

10 Potassium carbonate (powder, oven dried at 100°C under vacuum, 8.28g, 60 mmoles) was added to a solution of 3,5-dichlorosalicylaldehyde (11.46 g, 60 mmoles) in DMF (40 ml) at room temperature to give a bright yellow slurry. MEMCI (neat, 7.64 g, 61 mmoles) was then added while maintaining the bath temperature at 20°C. The mixture was then stirred at 15 22°C for 3 hours and MEMCI (0.3 g, 2.4 mmoles) was added. The mixture was stirred for another 0.5 hour and was poured into 200 mL of cold water to precipitate the product. The slurry was filtered on a pressure filter, the cake was washed with water (2 x 50 mL) and was dried under N₂/vacuum to afford the product (14.94 g, 89 %) as a pale yellow solid. ¹H NMR 20 (CDCl₃, TMS) 3.37 (s, 3H), 3.54 to 3.56 (m, 2H), 3.91 to 3.93 (m, 2H), 5.30 (s, 2H), 7.63 (d, 1H, J = 2.6 Hz), 7.73 (d, 1H, J = 2.6 Hz), 10.30 (s, 1H); ¹³C NMR (CDCl₃, TMS) (ppm): 59.03, 70.11, 99.57, 126.60, 129.57, 130.81, 132.07, 135.36, 154.66, 188.30. DSC: 31.17°C (endo 83.12 J/g);

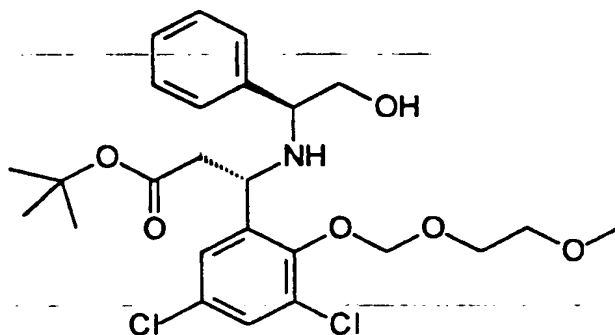
Microanalytical: calcd for C₁₂H₁₆Cl₂O₄:

25 C: 47.33%; H: 4.33%; Cl: 25.40%;
found: C: 47.15%; H: 4.26%; Cl: 25.16%.

5

Example 4

Preparation of



A 1 L jacketed 3 ports reactor with bottom valve, fitted with a
10 mechanical stirrer and an addition funnel was charged with the aldehyde
prepared in Example 3 (35 g, 0.125 mole) and THF (200 ml). The solution
was then stirred at 22°C and (S)-phenyl glycinol (17.20 g, 0.125 moles)
was added at once. After 0.5 hour of stirring at 22°C, magnesium sulfate
(15 g) was added at once. The mixture was then stirred for 1 hour at 22°C,
15 filtered and concentrated. The residue was diluted with NMP (100 ml) and
was used directly in the coupling.

A 1 L jacketed 3 ports reactor with bottom valve, fitted with a
mechanical stirrer and an addition funnel was charged with solid
Reformatsky reagent produced in Example 1 (91.3 g, 0.275 mole) and
20 NMP (200 ml). The solution was then cooled to -10°C and stirred at 350
rpm. The solution of imine in NMP was then added in 20 minutes while the
temperature was maintained at -5°C (jacket at -10°C). The reaction was
monitored by TLC (elution heptane/EtOAc 30%). After addition, the
mixture was stirred 1.5 hours at -8°C and 1 hour at -5°C. After cooling to
25 -10°C, a mixture of concentrated HCl/saturated solution of NH₄Cl (8.1
mL/200 ml) was added in 10 minutes. MTBE (200 ml) was added and the
mixture was stirred for 15 minutes at 23°C at 200 rpm. Stirring was
stopped and the layers were separated. The aqueous layer was extracted
with MTBE (100 ml). The two organic layers were combined, washed
30 successively with a saturated solution of NH₄Cl (100 ml), water (100 ml).

- 5 and brine (100 ml). The solution was dried with MgSO_4 (30 g), filtered and concentrated to afford an orange oil (66.26 g) (solidified on standing) containing the desired product as a single diastereoisomer (confirmed by ^1H , ^{13}C NMR).

- A sample was purified for analysis by recrystallization in heptane to
10 afford the desired product as an off white solid. ^1H NMR (CDCl_3 , TMS) (ppm) 1.45 (s, 9H), 2.53 (dd, 1H, $J = 9.5, 15.5$ Hz), 2.65 (dd, 1H, $J = 4.4, 15.5$ Hz), 3.02 (s(broad), 1H), 3.39 (s, 3H), 3.55 to 3.61 (m, 3H), 3.64 to 3.67 (m, 1H), 3.82 (d (broad), 1H, $J = 9.7$ Hz), 3.81 to 3.98 (m, 2H), 4.61 (dd, 1H, $J = 4.3, 9.4$ Hz), 5.14 (dd (AB syst.), 2H, $J = 6.2$ Hz), 7.07 (d, 1H, $J = 2.6$ Hz), 7.16 to 7.25 (m, 6H); ^{13}C NMR (CDCl_3 , TMS) (ppm): 27.91,
15 ~~42.21, 52.46, 58.85, 62.18, 65.66, 69.47, 71.55, 81.00, 98.94, 126.51,~~
~~127.10, 127.26, 127.99, 128.16, 128.52, 129.64, 139.45, 141.28, 150.14,~~
170.95; DSC: 43.74°C (endo, 54.59 J/g), 198.44°C (endo, 97.19 J/g), 235.42°C (endo., 59.40 J/g); $[\alpha]_{25}^D = + 8.7^\circ$ ($c = 1.057$, MeOH); IR (MIR)
20 (cm⁻¹) 1719.

Microanalytical: calcd for $\text{C}_{25}\text{H}_{33}\text{Cl}_2\text{NO}_6$:

C: 58.77%; H: 6.47%; N: 2.72%; Cl: 13.78%;

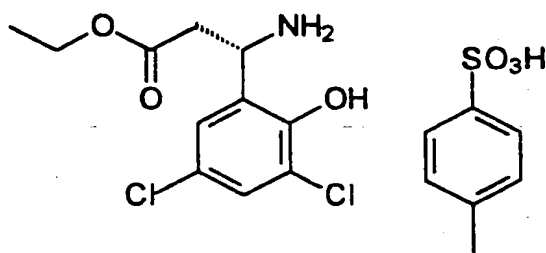
found: C: 58.22%; H: 6.54%; N: 2.70%; Cl: 13.66%.

Rf: 0.37 (EA 40%/Heptane 60%, UV and KMnO_4).

5

Example 5

Preparation of



10 A solution of crude ester prepared in Example 4 (17.40 g, 0.033 mole (theory)) in MeOH (250 ml) was charged to a 1L 3N jacketed reactor. The solution was cooled to 0°C and Pb(OAc)₄ [15 g, 0.033 mole] was added at once. After 2 hours, a 15% solution of NaOH (30 ml) was added and ethanol was removed under reduced pressure. Another 100 ml of

15 15% solution of NaOH was added and the mixture was extracted with MTBE (2 x 100 ml), washed with H₂O (2 x 100 ml) and brine (50 ml), dried with Na₂SO₄, filtered on celite and concentrated under reduced pressure to afford an orange oil (12.46 g) which was used without further purification. (R_f of intermediate 0.63) (EA 40%/heptane 60%, UV).

20 The oil was diluted with ethanol (30 ml) and paratoluene sulfonic acid (6.3 g, 0.033 mole) was added at once. The solution was then heated to reflux for 8 hours, cooled to room temperature and concentrated under reduced pressure. The residue was diluted with THF (20 ml) and was heated to reflux to form an homogeneous solution. The mixture was then

25 cooled to room temperature and the compound crystallized. Heptane (30 ml) and THF (10 ml) were added to form a fluid slurry which was then filtered. The cake was washed with THF/heptane(40 ml, 1/1) and was dried for 2 hours in a pressure filter under N₂/vacuum to afford a white solid (7.40 g). ¹H NMR (DMSO, TMS) (ppm) 1.12 (t, 3H, J = 7.1 Hz), 2.29

30 (s, 3H), 2.97 (dd (AAB), 1H, J = 7.4, 16.5 Hz), 3.04 (dd (AB), J = 7.0, 16.5 H), 4.05 (q, 2H, J = 7.1 Hz), 4.88 (t, 1H, J = 7.15 Hz), 7.11 (d, 2H, J = 7.8 Hz), 7.44 (9d, 2H, J = 2.5 Hz), 7.48 (d, 2H, J = 8.1 Hz), 7.58 (2H, d, J = 2.5

- 5 Hz), 8.15 (s (broad), 3H) and THF 1.76 (m, 0.25 x 4H), 3.60 (m, 0.25 x 4H);
 ^{13}C NMR (CDCl_3 , TMS) (ppm): 13.87, 21.35, 25.60, 36.28, 49.30, 61.42,
67.96, 123.52, 125.19, 125.47, 125.71, 125.84, 128.89, m 129.91, 140.57,
140.61, 149.19, 170.18 and THF 25.60, 67.96; DSC: 153.23°C (end., 61.26
J/g), 202.83°C (exo. 21.58 J/g), 288.83°C (133.6 J/g) $[\alpha]_{25}^D = +6.7^\circ$ (c =
10 1.063, CHCl_3); IR (MIR) (cm^{-1}) 3146, 2981, 2904, 1724, 1596, 1472.
Microanalytical: calcd for $\text{C}_{18}\text{H}_{21}\text{Cl}_2\text{NO}_6\text{S}$, 0.25 $\text{C}_4\text{H}_8\text{O}$:

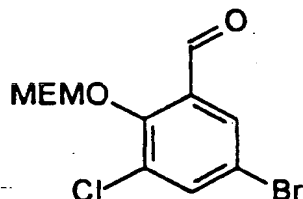
C: 48.73%; H: 4.95%; N: 2.99%; Cl: 15.14%

found: C: 48.91%; H: 4.95%; N: 2.90%; Cl: 14.95%.

5

Example 6

Preparation of

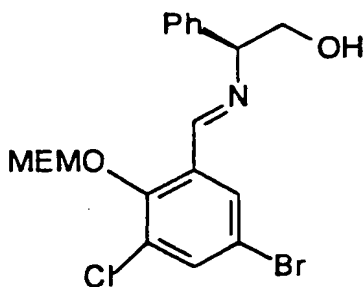


10 Potassium carbonate (powder, oven dried at 100°C under vacuum),
(22.1 g, 0.16 moles) was added to a solution of 3-chloro-5-
bromosalicylaldehyde (35.0 g, 0.15 moles) in DMF (175 ml) at room
temperature to give a bright yellow slurry. MEMCI (neat, 25.0 g, 0.2
moles) was added while maintaining the bath temperature at 20°C. The
15 mixture was then stirred at 22°C for 6 hours and was poured in 1200 mL of
DI water to precipitate the product. The slurry was filtered on a pressure
filter and the cake was washed with DI water (2 x 400 mL) and was dried
under N₂/vacuum to afford the product (46.0g, 95%) as an off white solid.
¹H NMR (CDCl₃, TMS) 3.35 (s, 3H), 3.54 to 3.56 (m, 2H), 3.91 to 3.93 (m,
20 2H), 5.30 (s, 2H), 7.77 (d, 1H), 7.85 (d, 1H), 10.30 (s, 1H); ¹³C NMR
(CDCl₃, TMS) (ppm): 59.05, 70.11, 71.49, 99.50, 117.93, 129.69, 129.78,
132.37, 138.14, 155.12, 188.22. DSC: 48.24°C (endo 90.51J/g);
Microanalytical: calcd for C₁₁H₁₂BrClO₄:
C: 40.82%; H: 3.74%; Cl: 10.95%; Br: 24.69%;
25 found: C: 40.64%; H: 3.48%; Cl: 10.99%; Br: 24.67%.

5

Example 7

Preparation of



The compound prepared in Example 6 (32.35 g, 0.1 mol) was charged in a 500 ml 3N round-bottom flask fitted with a mechanical stirrer, followed by THF (160 ml) and (S)-phenylglycinol (13.71 g, 0.1 mol) was added. After 30 minutes at 22°C, MgSO₄ (20 g) was added. The mixture was stirred for 1 hour at 22°C and filtered on a coarse fritted filter. The filtrate was concentrated under reduced pressure to afford a pale yellow oil (48.0 g) containing the imine. No further purification was performed and the crude product was used directly in the coupling reaction.

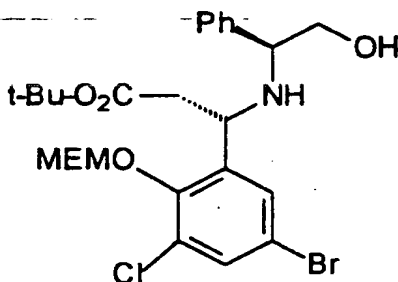
Microanalytical: calcd for C₁₉H₂₁BrClNO₄:

C: 51.54%; H: 4.78%; N: 3.16%; Br: 18.04%; Cl: 8.00%

found: C: 51.52%; H: 5.02%; N: 2.82%; Br: 16.31%; Cl: 7.61%.

Example 8

Preparation of



- In a 5L 3N round-bottom flask fitted with a mechanical stirrer,
- 10 Reformatsky reagent from Example 1 (332.0 g, 0.8 mol) was taken up in NMP (660 mL) under nitrogen. The solution was then cooled to -10°C. A solution of imine (0.4 mol) prepared in Example 7 in NMP (320 ml) was prepared under nitrogen and then added in 30 minutes to the above reaction mixture while the temperature was maintained at -5°C. The
- 15 mixture was stirred for one hour at -8°C and at -5°C for 2 hours and cooled to -10°C. A mixture of concentrated HCl/saturated solution of NH₄Cl (30 mL/720 mL) was added in 10 minutes. The reaction mixture was stirred for 30 additional minutes. MTBE (760 ml) was added and the mixture was stirred for 1 hour at 23°C. Stirring was stopped and the layers were
- 20 separated. The aqueous layer was extracted with MTBE (320 ml). The two organic layers were combined, washed successively with a saturated solution of NH₄Cl (320 ml), DI water (320 ml) and brine (320 ml). The solution was dried with MgSO₄ (60 g), filtered and concentrated to afford a yellow oil (228 g) containing the desired product as a single
- 25 diastereoisomer.

DSC; 227.54°C (endo. 61.63 J/g);

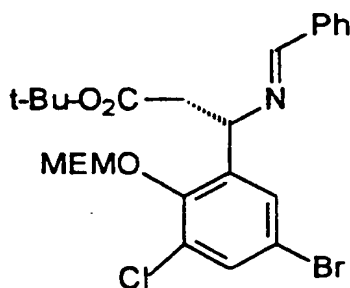
Microanalytical calcd for C₂₅H₃₃BrClNO₆:

C: 53.72%; H: 5.95%; N: 2.50%; Br: 14.29%; Cl: 6.33%

found: C: 53.80%; H: 6.45%; N: 2.23%; Br: 12.85%; Cl: 6.12%.

Example 9

Preparation of



A solution of crude ester prepared in Example 8 (~111.0 g) in
10 methanol (1500 mL) was charged under nitrogen atmosphere to a 3L 3N
round-bottom flask fitted with a mechanical stirrer. The reaction mixture
was cooled to 0°C and lead tetraacetate (88.67 g, 0.2 mol) was added in
one portion. The reaction mixture was stirred for 3 hours at 0°C and then
15 5°C. Methanol was removed under reduced pressure on rotavap. Another
600 mL of 15% aqueous NaOH was added and the reaction mixture was
extracted with (2 X 300 mL) ethylacetate and (2 X 200 mL) MTBE and (2 X
200 mL) ethylacetate. Organic layers were combined and washed with (2
X 200 mL) DI water and (2 X 100 mL) brine and dried over anhydrous
20 MgSO₄ (30 g). The solution was filtered over celite and concentrated
under reduced pressure to give the desired product (96 g) as an orange
oil.

DSC: 233.60°C (endo. 67.85 J/g);

Microanalytical: calcd for C₂₄H₂₉BrClNO₅:

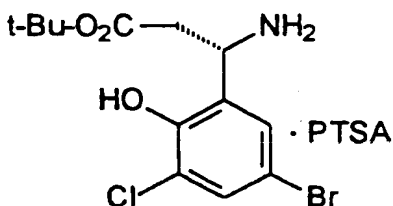
25 C: 54.71%; H: 5.54%; N: 2.65%; Br: 15.16%; Cl: 6.72%

found: C: 52.12%; H: 5.40%; N: 2.47%; Br: 14.77%; Cl: 6.48%.

5

Example 10

Preparation of



Crude product prepared in Example 9 (~94 g), was taken in
 10 absolute ethanol (180 mL) and para toluenesulfonic acid monohydrate
 (50.0 g, 0.26 mol) was added. The reaction mixture was then heated to
 reflux for 8 hours after which the solvent was removed under reduced
 pressure. Residual solid was taken up in THF (100 mL) and the THF was
 then stripped off under reduced pressure. Residue was dissolved in
 15 ethylacetate (500 mL) and cooled to ~5°C. Solid was filtered and washed
 with (2 X 50 mL) heptane to give a white solid. The solid was air dried to
 give the desired product (38 g) as a single isomer as a white solid.
¹H NMR (DMSO, TMS) (ppm) 1.12 (t, 3H), 2.29 (s, 3H), 3.0 (m, 2H), 4.05
 (q, 2H), 4.88 (t, 1H), 7.11 (d, 2H), 7.48 (d, 2H), 7.55 (d, 1H), 7.68 (1H, d),
 20 8.35 (br. s, 3H); ¹³C NMR (DMSO, TMS) (ppm): 13.82, 20.75, 37.13, 45.59,
 60.59, 110.63, 122.47, 125.44, 127.87, 128.06, 129.51, 131.95, 137.77,
 145.33, 150.14, 168.98; DSC: 69.86°C (endo 406.5 J/g), 165.72°C (end.
 62.27 J/g), 211.24°C (exo. 20.56 J/g). [α]₂₅^D = + 4.2° (c = 0.960, MeOH); IR
 (MIR) (cm⁻¹) 2922, 1726, 1621, 1591, 1494, 1471, 1413, 1376, 1324,
 25 1286, 1237, 1207;.

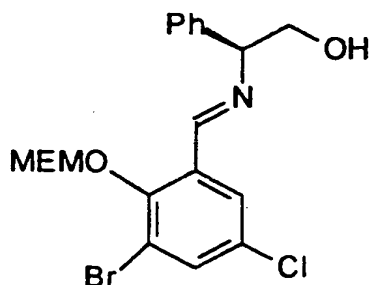
Microanalytical: calcd for C₁₈H₂₁BrClNO₆S:

C: 43.69%; H: 4.27%; N: 2.83%; Br: 16.15%; Cl: 7.16%; S: 6.48%
 found: C: 43.40%; H: 4.24%; N: 2.73%; Br: 16.40%; Cl: 7.20%; S: 6.54%.

5

Example 11

Preparation of



MEM protected 3-bromo-5-chlorosalicylaldehyde (129.42 g, 0.4 mol)
10 was charged in a 2000 ml 3N round-bottom flask fitted with a mechanical
stirrer, followed by addition of THF (640 ml) and (S)-phenylglycinol (54.86
g, 0.4 mol). After 30 minutes at 22°C, MgSO₄ (80 g) was added. The
mixture was stirred for 2 hours at 22°C, and filtered on a coarse fritted
filter. The filtrate was concentrated under reduced pressure to afford a
15 pale yellow oil (180.0 g) containing the imine. No further purification was
performed and the crude product was used directly in the coupling
reaction. Microanalytical: calcd for C₁₉H₂₁BrClNO₄:

C: 51.54%; H: 4.78%; N: 3.16%; Br: 18.04%; Cl: 8.00%

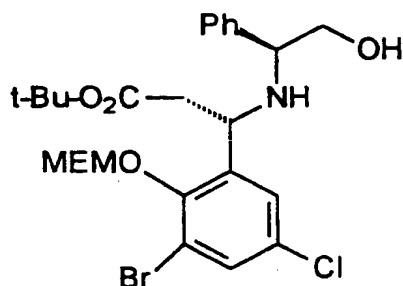
found: C: 50.22%; H: 4.94%; N: 2.93%; Br: 17.15%; Cl: 7.56%.

20

5

Example 12

Preparation of



In a 5L 3N round bottom flask fitted with a mechanical stirrer,
10 reagent from Example 1 (332.0 g, 0.8 mol) was taken up in NMP (660 mL)
under nitrogen. The solution was then cooled to -10°C. A solution of
imine (180 g, 0.4 mole) prepared in Example 11 in NMP (320 ml) was
prepared under nitrogen and then added in 30 minutes to the above
reaction mixture while the temperature was maintained at -5°C. The
15 mixture was stirred for an additional hour at -8°C and at -5°C for 2 hours
after addition was complete. The mixture was cooled to -10°C. A mixture
of concentrated HCl/saturated solution of NH₄Cl (30mL/720 mL) was
added over 10 minutes. MTBE (760 ml) was added and the mixture was
stirred for 30 minutes at 23°C. Stirring was stopped and the layers were
20 separated. The aqueous layer was extracted with MTBE (320 ml). The
two organic layers were combined, washed successively with a saturated
solution of NH₄Cl (320 ml), DI water (320 ml) and brine (320 ml). The
solution was dried with MgSO₄ (60 g), filtered and concentrated to afford a
yellow oil (221.0 g) containing the desired product as a single
25 diastereoisomer.

DSC: 211.80°C (endo. 72.56 J/g), 228.34°C (98.23 J/g);

Microanalytical: calcd for C₂₁H₃₃BrClNO₆:

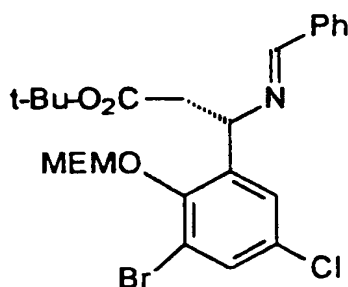
C: 53.72%; H: 5.95%; N: 2.50%; Br: 14.29%; Cl: 6.33%

found: C: 52.11%; H: 6.09%; N: 2.34%; Br: 12.84%; Cl: 6.33%.

5

Example 13

Preparation of



A solution of crude ester prepared in Example 12 (~111 g), in
10 methanol (1500 mL) was charged under argon atmosphere to a 3L 3N
round-bottom flask fitted with a mechanical stirrer. The reaction mixture
was cooled to 0°C and lead tetraacetate (88.67 g, 0.2 mol) was added in
one portion. The reaction mixture was stirred for 3 hours at 0°C and then
15 15% aqueous NaOH (150 mL) was added to the reaction mixture below
5°C. Methanol was removed under reduced pressure on rotavap.
Additional 15% aqueous NaOH (150 ml) was added and the reaction
mixture was extracted with ethylacetate (3 X 300 mL) and washed with DI
(2 X 100 mL) water and brine (2 X 100 mL) and dried over anhydrous
MgSO₄ (30 g). The mixture was then filtered over celite and concentrated
20 under reduced pressure to give the desired product (103 g) as a red oil.
DSC: 197.82°C (exo.), 204.17°C, 213.24°C and 225.38°C (endo.),
Microanalytical: calcd for C₂₄H₂₉BrClNO₅:

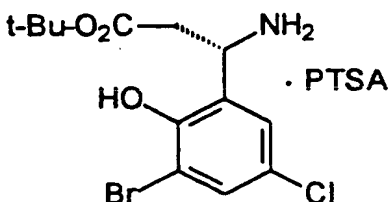
C: 54.71%; H: 5.54%; N: 2.65%; Br: 15.16%; Cl: 6.72%

found: C: 50.13%; H: 5.21%; N: 2.39%; Br: 13.98%; Cl: 6.21%.

5

Example 14

Preparation of



10 Crude product from Example 13 (~102.0 g) was taken up in absolute ethanol (180 mL) and para toluenesulfonic acid monohydrate (50 g, 0.26 mol) was added. The reaction mixture was then heated to reflux for 8 hours after which the solvent was removed under reduced pressure. Residual solid was taken up in THF (100 mL) and the THF was then
15 stripped off under reduced pressure. The residue was dissolved in THF (200 mL) on warming to 40°C. Heptane (400 mL) was added and the reaction mixture was cooled to 30°C. A thick slurry precipitated out which was filtered with 1:1 THF/heptane solution (200 mL). The solid was washed with acetone (3 X 100 mL) and dried under vacuum at 40 psi
20 under a blanket of nitrogen at 48°C-49°C for 16 hours to afford the desired product (55 g) as a white solid. ¹H NMR (DMSO, TMS) (ppm) 1.14 (t, 3H), 2.29 (s, 3H), 3.0 (m, 2H), 4.05 (q, 2H), 4.9 (t, 1H), 7.11 (d, 2H), 7.48 (dd, 3H), 7.70 (d, 1H), 8.35 (br. s, 3H); ¹³C NMR (DMSO, TMS) (ppm): 13.82, 20.76, 37.20, 45.76, 60.60, 112.47, 124.08, 125.45, 127.21, 127.63,
25 128.10, 132.19, 137.88, 145.19, 150.73, 168.98; DSC: 146.19°C (endo.), 178.15°C (end., 68.66 J/g), 210.63°C (exo.); [α]₂₅^D = + 6.3° (c = 1.110, MeOH); IR (MIR) (cm⁻¹) 3036, 2980, 2903, 2857, 1722, 1595, 1486, 1467, 1419, 1376;.

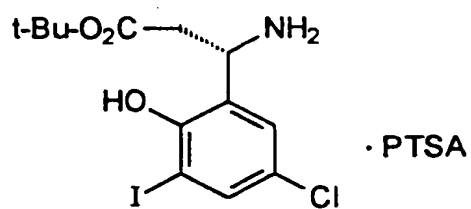
Microanalytical: calcd for C₁₈H₂₁BrClNO₆S:

30 C: 43.69%; H: 4.27%; N: 2.83%; Br: 16.15%; Cl: 7.16%; S: 6.48%
found: C: 44.47%; H: 4.46%; N: 2.66%; Br: 15.15%; Cl: 7.05%; S: 6.52%.

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Example 15

Preparation of



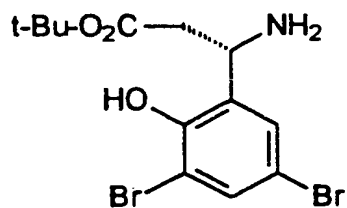
10

The above compound was prepared using procedures analogous to those described herein substituting the appropriate starting materials.

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Example 16

Preparation of



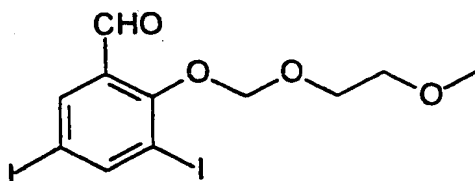
10

The above compound was prepared using procedures analogous to those described herein substituting the appropriate starting materials.

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Example 17

Preparation of 2-O-(MEM)-3,5-diiodosalicylaldehyde



10

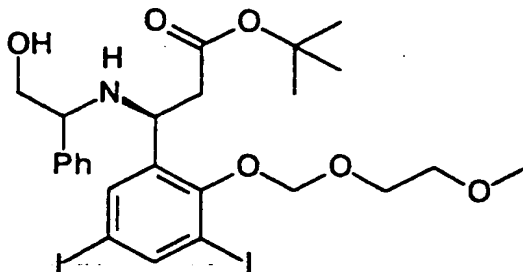
Potassium carbonate (18.5 g, 0.134 mole) was added to a solution of 3,5-diiodosalicylaldehyde (50.0 g, 0.134 mole) in DMF (150 mL) at 20°C. This resulted in a yellow slurry and MEM-Cl (15.8 mL, 0.134 mole) was added maintaining the reaction temperature. After 2 hours, additional MEM-Cl (1.5 g) was added. After stirring for a further 1 hour, the reaction mixture was poured into ice-water and stirred. The precipitate formed, was filtered, and dried *in vacuo* to afford the desired protected aldehyde (61 g, 99% yield). ¹H NMR was consistent with the desired product.

15

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Example 18

Preparation of

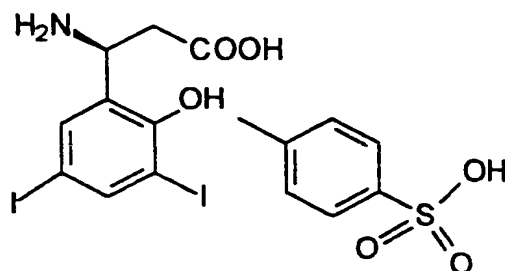


10 (S)-phenyl glycinol (17.9 g, 0.13 mole) was added to a solution of 2-O-(MEM)-3,5-diiodosalicylaldehyde (41.5 g, 0.112 mole) in THF (150 mL) at room temperature. After 1 hour of stirring MgSO_4 (20.7 g) was added and the stirring was continued for 2 hours. The reaction mixture was filtered and the filtrate was concentrated and dried *in vacuo* for 2 hours. A
15 2-neck round bottomed flask was charged with the Reformatsky reagent (96 g, 0.289 mole) and N-methylpyrrolidone (250 mL) and was stirred at -10°C . A solution of the imine in N-methylpyrrolidone (100 mL) was slowly added maintaining the temperature at -10°C . The mixture was maintained at this temperature for 2 hours and for 1 hour at -5°C . After cooling the
20 reaction mixture to -10°C , a solution of concentrated HCl in saturated ammonium chloride (16 ml/200 mL) was added. Ethyl ether (500 mL) was added and the mixture was stirred for 2 hours at room temperature. The ether layer was separated, and the aqueous layer further extracted with ether (300 mL). The combined ether layers was washed with saturated
25 ammonium chloride (200 mL), water (200 mL), brine (200 mL), dried (MgSO_4) and concentrated to afford an oil (90.0 g, 99% yield). NMR indicated desired product and one diastereomer.

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Example 19

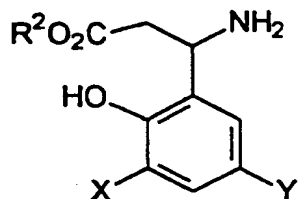
Preparation of



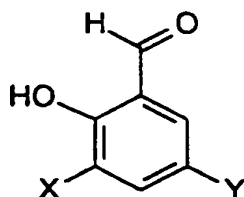
A solution of the crude ester from Example 18 (14.0 g, 20.1 mmol) was dissolved in ethanol (100 mL) and was cooled to 0°C. Lead tetraacetate (9.20 g, 20.75 mmol) was added in one lot. After 3 hours, 15% solution of NaOH (73 mL) was added to the reaction mixture. Most of the ethanol was removed under reduced pressure. The residue was added to a 15% solution of NaOH (200 mL) which was extracted with ether (400 mL). The ether layer was washed with water (100 mL), brine (100 mL), dried and concentrated to afford an orange oil. This was dissolved in ethanol (100 mL) and para-toluenesulfonic acid (6.08 g) was added. The solution was heated at reflux for 8 hours and was concentrated under reduced pressure. The residue was diluted with THF (60 mL), was heated at reflux and was cooled. Upon storage, no precipitate formed. The reaction mixture was concentrated and purified by preparative hplc to afford the amino acid as its PTSA salt. The solid obtained was dissolved in ethanol and was saturated with HCl gas. The reaction mixture was heated at reflux for 6 hours. The reaction mixture was concentrated to afford the PTSA salt of the desired amino acid (12.47 g) as its ethyl ester.

What is claimed is:

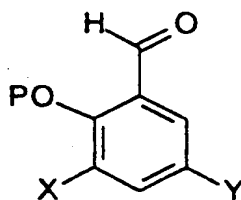
1. A process for the preparation of chiral β -amino acids of the formula



wherein X and Y are the same or different halo group; wherein R^2 is H or lower alkyl which process comprises reacting a 3,5-dihalosalicylaldehyde of the formula



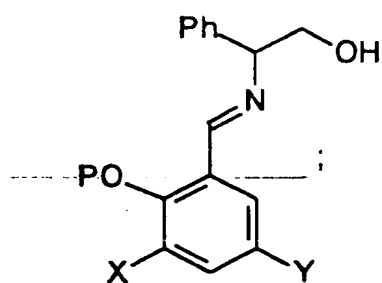
with MEMCl or BnBr to produce a protected 3,5-dihalosalicylaldehyde of the formula



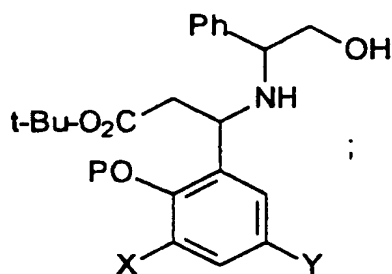
where P is Bn or MEM;

treating the protected 3,5-dihalosalicylaldehyde with (R) or (S) phenylglycinol in THF or toluene to produce an imino alcohol of the formula

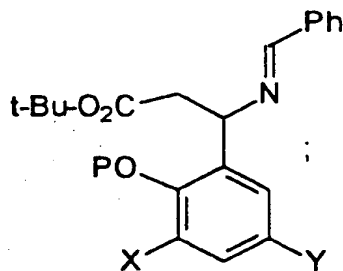
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reacting said imino alcohol with $\text{BrZnCH}_2\text{CO}_2\text{-t-Bu}$ in NMP, DMSO or THF to produce an amino alcohol of the formula

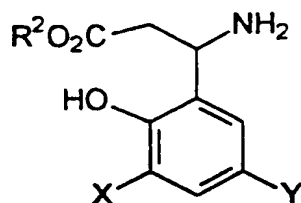


reacting the amino alcohol with lead tetraacetate, sodium periodate or periodic acid to produce an imine of the formula



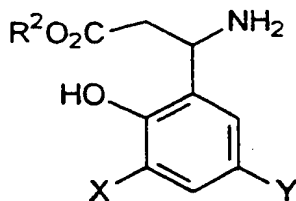
transesterifying, deprotecting and hydrolyzing said imine and isolating a chiral product of the formula

47



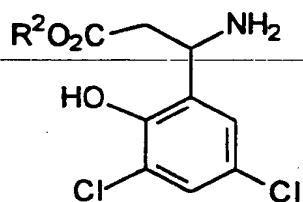
or an acid addition salt thereof.

2. The process according to Claim 1 wherein X is Cl and Y is Cl.
3. The process according to Claim 1 wherein X is Cl and Y is Br.
4. The process according to Claim 1 wherein X is Br and Y is Cl.
5. The process according to Claim 1 wherein X is I and Y is Cl.
6. The process according to Claim 1 wherein X is Br and Y is Br.
7. The process according to Claim 1 wherein X is I and Y is I.
8. The process according to Claim 1 wherein X is Cl and Y is I.
9. The process according to Claim 1 wherein X is Br and Y is I.
10. The process according to Claim 1 wherein X is I and Y is Br.
11. A compound of the formula

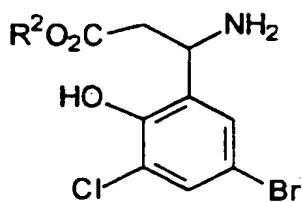


wherein X and Y are the same or different halo groups; R^2 is H or lower alkyl or acid addition salts thereof.

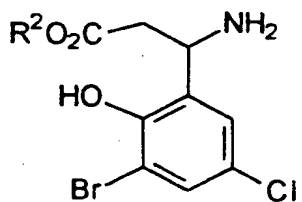
12. A compound according to Claim 11 wherein the compound is of the formula



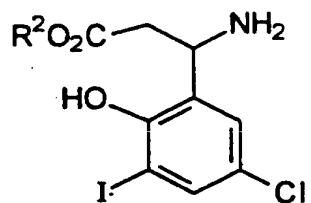
13. A compound according to Claim 11 wherein the compound is of the formula



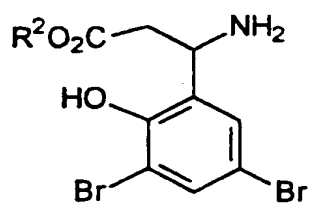
14. A compound according to Claim 11 wherein the compound is of the formula



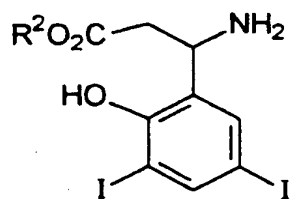
15. A compound according to Claim 11 wherein the compound is of the formula



16. A compound according to Claim 11 wherein the compound is of the formula



17. A compound according to Claim 11 wherein the compound is of the formula





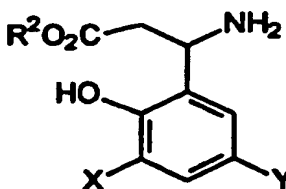
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(21) International Application Number: PCT/US99/03280 (22) International Filing Date: 22 February 1999 (22.02.99) (30) Priority Data: 60/076,710 4 March 1998 (04.03.98) US (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): COLSON, Pierre-Jean [FR/US]; Apartment 1A, 10104 Old Orchard Road, Skokie, IL 60076 (US). AWASTHI, Alok, K. [IN/US]; 9438 Keystone Avenue, Skokie, IL 60076 (US). NAGARAJAN, Srinivasan, R. [US/US]; 16209 Forest Meadows Drive, Chesterfield, MO 63005 (US). (74) Agents: KOVACEVIC, Cynthia, S. et al.; G.D. Searle & Co., P.O. Box 5110, Chicago, IL 60680-5110 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 11 November 1999 (11.11.99)	

(54) Title: SYNTHESIS OF CHIRAL β -AMINO ACIDS

(57) Abstract

The invention herein is directed to a process for the preparation of chiral β -amino acids and esters of formula (I), wherein X and Y are the same or different halo groups, R² is H or lower alkyl and isomers and pharmaceutically acceptable salts thereof.



(I)

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International Application No

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A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07C227/32 C07C229/34		
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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 08145 A (G.D. SEARLE & CO.;USA) 6 March 1997 (1997-03-06) page 375 -page 388 page 468 -page 469 page 650 -page 652 page 675 -page 683 ---	12-16
X	WO 98 02410 A (CAIN JANICKI KIMBERLY J ;BOYS MARK L (US); KNABLE CARL M (US); NUG) 22 January 1998 (1998-01-22) page 13 -page 17 claim 6 --- <div style="text-align: center;">-/--</div>	1-11
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	N.N. SUVOROV ET AL.: "Thyroid gland hormones and their analogs" ZH. OBSHZH. KHIM. (ENGLISH EDITION), vol. 28, 1958, pages 1430-1432, XP002116116 page 1430 page 1431, last paragraph ---	17
A	MOKHALLALATI M K ET AL: "LEAD TETRAACETATE CLEAVAGE OF CHIRAL PHENYLGLYCINOL DERIVED SECONDARY AMINES WITHOUT RACEMIZATION" SYNTHETIC COMMUNICATIONS, vol. 23, no. 14, 1 January 1993 (1993-01-01), pages 2055-2064, XP002043791 ISSN: 0039-7911 the whole document ---	1
A	MOKHALLALATI M K ET AL: "AN EFFICIENT ENANTIOMERIC THREE STEP SYNTHESIS OF BETA-AMINO ACIDS (ESTERS)" TETRAHEDRON LETTERS, vol. 34, no. 1, 1 January 1993 (1993-01-01), pages 47-50, XP002043790 ISSN: 0040-4039 the whole document -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/03280

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